

REMARKS

Claims 2 - 17, 25, 29, 38, 44-61, and 65 - 107 are pending.

Claims 4 - 17, 25, 29, 38, 44-61, 66 - 73, 79-89, 98 - 105 and 107 have been withdrawn.

Newly added Claim 106 is generic.

Claims 2 and 106 are the only independent claims.

The specification has been amended at page 7 to rephrase the incorporation of the parent application in a clearer and more traditional wording.

One of the two Claims 82 that were listed in the last amendment has been represented as Claim 107.

Claim 65 which had been found allowable has been amended to recite all the limitations of its parent Claim 2.

Claim 2 has been amended to recite a limitation excluding superoxide dismutase (SOD) mimics. New claim 106 also recites this limitation.

Support for the amendment can be found throughout the specification and more particularly at:

page 11, line 1,

page 62, lines 14 - 15,

page 63, line 15,

page 66, line 9 and 23,

page 67, line 16, and

page 68, line 5.

Parent US Patent No. 5,906,996 Murphy (Murphy) that has been incorporated in this application by reference (see page 7, line 23) also provides numerous references to the SOD inhibiting role of the claimed preparations as will be demonstrated below.

Since 5,610,293 RILEY and all (Riley), the only prior art cited against the claims, only recognizes SOD mimics as effective in the treatment of various inflammatory diseases, the amendment is deemed sufficient to take the claims beyond the scope of 35 USC 102 (b).

The following material may not be particularly necessary to overcome the pending rejection, but is offered to help the examiner appreciate the novelty and non-obviousness of the invention, and to quell any eventual 35 USC 103(a) rejection.

I. Riley describes the synthesis of pentamine SOD mimics. By contrast the present patent application discloses and claims the composition, synthesis and utility of polyamines and substituted polyamines, which have amongst other properties that of not relying upon SOD activation, but in many instances exhibit SOD inhibition. The substitution reactions to add the side groups in the compounds are different. Riley states that pentamine SOD mimics can be utilized to treat inflammatory diseases and list diabetes mellitus amongst many other diseases as an example of an inflammatory disease, without any prior art or experimental demonstration of effective treatment of diabetes by this type of compounds. Riley does not disclose or suggest either a treatment for diabetes nor the composition nor any therapeutic utility of any tetramine cyclam compounds. Instead it discloses a diametrically opposite biological action of a different group of compounds from the compositions claimed in the instant patent application, namely, SOD mimics.

Riley seems to exclude the small size ring compounds of the invention in Column 86 lines 54 - 61 in the following terms:

"Manganese(II) complexes of 15-membered macrocyclic ligands containing only four nitrogens (Examples 17, 18 and 21) do not have SOD activity. Other manganese(II) complexes with less than or greater than 15-membered macrocyclic ligands with less than five or greater than five nitrogens (Examples 10,13,14,20 and 25) are not catalysts for the dismutation of superoxide."

Thus, Riley teaches away from the invention and buttresses the non-obviousness of the claimed tetramine cyclam compounds that have no effective SOD activity.

II. Murphy states the following in discussing the role of superoxide dismutase:

In column 2, lines 38-45 and in column 7, lines 1-11:

"High levels of CuZn SOD were demonstrated immunohistochemically in the large pyramidal cells of control and Alzheimer's disease patients brains (Delacourte A. et al 1988). The localization of the superoxide dismutase gene on chromosome twenty one and the early occurrence of Alzheimer's Disease in Down's syndrome suggest that superoxide dismutase activity and hydrogen peroxide formation may contribute to Alzheimer's pathogenesis. Also the neurons containing high levels of NADPH diaphorase are relatively spared in neonatal hypoxia and hypoglycemia but are affected in Alzheimer's disease."

In column 7, lines 17-30:

Superoxide is an inhibitor of catalase and glutathione peroxidase. Superoxide and hydroxyl radicals inhibit catalase, hydrogen peroxide and hydroxyl radicals inhibit glutathione peroxidase and hydrogen peroxide inhibits superoxide dismutase (Pigeolet E et al).

The enzymatic system in the basal ganglia operates within the following constraints; Age dependent and disease associated decline of the enzymes activities which remove hydrogen peroxide occurs especially in capillaries and therefore the capacity of the protective enzymes may be overrun by over activating copper and manganese dependent superoxide dismutases. The enzymes are active only within limited ranges as excess substrate or product will inhibit them."

In column 7, lines 34-46:

"The phenomenology of Parkinson's disease includes excess oxidized iron and copper displacement. The physiological framework of the melanin and lipofuscin containing nuclei with low levels of glutathione peroxidase and catalase which enzymes are inhibited by excess of superoxide substrate or products indicates that only limited shifts of redox activity in either direction are permissible. NADPH diaphorase may protect these nuclei from oxidative stress as in neonatal anoxia but renders them more vulnerable to reducing agents. Superoxide and hydroxyl radicals inhibit catalase, hydrogen peroxide and hydroxyl radicals inhibit glutathione peroxidase and hydrogen peroxide inhibits superoxide dismutase (Pigelet E et al). "

In column 14, lines 16-27:

"More specifically these compounds can provide:

g) Inhibition of superoxide dismutase, amine oxidase, monoamine oxidase B;"

In column 15, lines 1-17:

"Given the constraints evident from the use of xenobiotics and chelates which disturb subcellular metal compartmentation and the inflexibility of the redox enzyme system, an effective compound would need to remove excess copper from tyrosinase, superoxide dismutase, monoamine oxidase B, amine oxidase and also the iron excess which displaces copper from storage sites in idiopathic Parkinsonism. It must not be a direct superoxide dismutase inhibitor or thiol containing reducing agent. Triethylene tetramine does reduce superoxide dismutase activity without oxidizing glutathione (Kelner M.J. et al 1989)."

In column 17, lines 39-52:

"The radical scavenging and reducing agents (in consequence of oxidizing redox metals) TEMPO and PBN were used as a further test of MPTP's behavior as a reducing or oxidizing

compound. The effects of the xenobiotic MPTP alone and in combination with spin traps / spin labels TEMPO (2,2,6,6-tetramethylpiperidine-N-oxyl), at 0.1 mM, 0.25 mM and 1.0 mM doses, and PBN (N-tert-butyl-a-phenylnitron), at 0.18 mM and 1.7 mM doses, preloading the animals one hour prior to MPTP administration, indicated their patterns of effects on these amine precursor hydroxylations. MPTP decreased dopamine levels, and increased norepinephrine and serotonin levels, whereas TEMPO and PBN decreased norepinephrine, serotonin and dopamine levels. Administered alone they reduced pigmentation density."

In column 17, lines 54-57:

PBN in combination with MPTP dropped dopamine levels to about 10 percent of baseline. Toxicity was dose dependent and cumulative for both PBN and MPTP. TEMPO likewise decreased dopamine more than MPTP alone. TEMPO toxicity was less dose dependent."

In column 17, lines 61-67:

PBN at 0.18 mMolar partially reverses the MPTP effect of elevating norepinephrine by decreasing it to eighty percent at times less than four hours. This corresponds with the time of PBN maximal effect.

TEMPO 0.1 mMolar had little effect on MPTP induced norepinephrine elevation at 3 hours in contrast with PBN, but does lower norepinephrine to baseline by thirteen hours."

In column 18, lines 3-6:

PBN at low and high doses in combination with MPTP was not protective against MPTP induced elevation in serotonin. Likewise TEMPO was not protective at low or high doses.

In the four last quoted sections, and the associated drawings, Murphy demonstrates the ineffectiveness and toxicity of SOD mimicking compounds TEMPO (2,2,6,6-

tetramethylpiperidine-N-oxyl) and PBN (N-tert-butyl-a-phenylnitron) in MPTP induced Parkinsonism by contrast with the therapeutic effectiveness of 2,3,2 tetramine which is a partial SOD inhibitor.

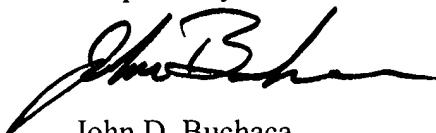
Instead, Murphy identifies SOD inhibition as being valuable in the treatment of neurodegeneration.

Having exposed unequivocally the reasons why excessive SOD activity contributes to neurodegenerative disease and by implication the inappropriateness of SOD mimics as a treatment therefore, it extols the value of limited inhibition of SOD in the treatment of neurodegenerative disease by binding excess free copper. Nowhere does Murphy or the instant application propose that SOD mimics would be an appropriate therapeutic for neurodegeneration.

In conclusion, it is apparent that Riley does not anticipate the claimed inventions, and in fact, supports their non-obviousness by teaching a contrary treatment of inflammatory diseases.

In view of the above, an early allowance of all the pending claims is earnestly solicited.

Respectfully submitted.

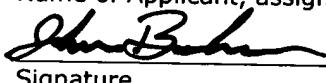


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